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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/577,341	BIANCHI ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-137* is/are pending in the application.

4a) Of the above claim(s) *128-137* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/10/07 and 9/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-127 in the reply filed on December 19, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-137 are pending.

Claims 1-127 have been examined herein.

Claims 128-137 are withdrawn from further consideration as being drawn to a nonelected invention.

Claim Objections

3. Claim 95 is objected to because a "." should be inserted following "Red™". See MPEP 608.01(m).

4. The use of the trademarks CY-3, CY-5, SPECTRUM RED, and SPECTRUM GREEN have been noted in this application. The trademark(s) should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-18, 47-50, 92-95 and 110-113 contain the trademarks/trade names "Cy-3™", "Cy-5™", Spectrum Red™, and "Spectrum Green ™." Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a fluorescent label and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6, 12-15, 19, 22, 25-26, 28-31, 34, 35 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Bianchi (Clinical Chemistry. Oct. 2001. 47: 1867-1869; cited in the IDS of May 10, 2007).

Bianchi teaches a method of prenatal diagnosis comprising: i) providing a sample of amniotic fluid fetal DNA; ii) analyzing the amniotic fluid fetal DNA by hybridization to obtain fetal genomic DNA; and iii) based on the fetal genomic information, providing a

prenatal diagnosis (page 1867, col. 2 and page 1868, col. 1). In particular, Bianchi teaches obtaining an amniotic fluid sample from pregnant woman at 16-20 weeks of gestation, isolating DNA present in the amniotic fluid sample, performing real-time quantitative PCR using primers and a dual-labeled fluorescent TaqMan probe, and determining the sex of the fetus, thereby providing a prenatal diagnosis. Bianchi teaches that amniotic fluid contains 100 to 200 fold more fetal DNA per millimeter as compared to maternal plasma.

Regarding claim 2, Bianchi teaches that the amniotic fluid fetal DNA is obtained by providing the amniotic fluid sample from a pregnant woman, removing cells from the sample by centrifugation, and treating the remaining amniotic fluid so as to extract cell-free DNA (page 1867, col. 2).

Regarding claim 3, the centrifugation step removes substantially all of the cells from the amniotic fluid so that the amniotic fluid fetal DNA consists essentially of cell-free fetal DNA.

Regarding claim 5, Bianchi teaches that the amniotic fluid samples are first frozen, stored under appropriate conditions, and thawed at 37C prior to vortexing and treating to extract DNA (page 1867, col. 2).

Regarding claim 6, Bianchi teaches that after thawing, the samples are centrifuges to remove any remaining cells (page 1867, col. 2).

Regarding claims 12-13 and 19, Bianchi teaches amplifying the amniotic fluid fetal DNA by PCR using primers (page 1868, col. 1).

Regarding claims 14-15, Bianchi teaches hybridizing the fluorescently labeled TaqMan probe to the amplified amniotic fluid fetal DNA to produce labeled amniotic fluid fetal DNA (page 1868, col. 1).

Regarding claim 22, Bianchi teaches that the prenatal diagnosis comprises determining the sex of the fetus (page 1868 and Table 1).

Regarding claims 25, 26, 28-30, 34, and 35, in the method of Bianchi, the amniotic fluid samples were collected in cases in which the fetus was suspected to have a chromosomal abnormality as indicated by an advanced maternal age, abnormal maternal serum screening results, or detection of a fetal sonographic abnormality. In two of the fetuses, the chromosomal abnormality was trisomy 21 associated with Down syndrome (page 1868, col. 1 and Table 1).

Regarding claims 31 and 38, since the amniotic fluid was obtained from subjects having high levels of biochemical markers in maternal serum, the fetuses were at risk of a disease or condition not detectable by G-banding analysis of metaphase CGH.

7. Claims 1, 2, 4, 14-17, 19, 21-26, 28-31, 33, 34, 35 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Lapierre et al (Prenatal Diagnosis. 2000. 20: 123-131; cited in the IDS of September 13, 2007).

Lapierre teaches a method of prenatal diagnosis comprising: i) providing a sample of amniotic fluid fetal DNA; ii) analyzing the amniotic fluid fetal DNA by hybridization to obtain fetal genomic DNA; and iii) based on the fetal genomic information, providing a prenatal diagnosis (pages 124-125). In particular, Lapierre teaches obtaining an amniotic fluid sample from pregnant woman at 14-35 weeks of

gestation, isolating DNA present in the amniotic fluid sample, labeling the DNA using Cyanine 3 (Cy3) and Fluor X-Amido using nick translation and subjecting the labeled DNA to comparative genomic hybridization (CGH) analysis using normal male metaphase chromosomal probes (page 124), and determining the karyotype of the fetus, as well as the sex of the fetus, thereby providing a prenatal diagnosis (pages 124-125 and Table 1).

Regarding claims 2 and 4, Lapierre teaches that a first portion of the sample comprising amniotic cells is removed (i.e., removing cell populations from the sample) to obtain a remaining amniotic material and treating the remaining 5-10 ml of amniotic fluid to extract high molecular weight DNA for CGH analysis (page 124, col. 1). The remaining amniotic fluid thereby contained both amniotic cells and cell free fetal DNA.

Regarding claims 14-17 and 19, Lapierre teaches labeling the amniotic fluid fetal DNA by nick translation using the fluorescent label Cy-3 (page 124, col. 2) Bianchi teaches that the amniotic fluid samples are first frozen, stored under appropriate conditions, and thawed at 37C prior to vortexing and treating to extract DNA (page 1867, col. 2).

Regarding claims 21, 23, 24 , 28-30, 33-35, Lapierre teaches that the prenatal diagnosis comprises detecting trisomy 13, 18 or 21 (Table 1) and the presence of the XX or XY chromosomes.

Regarding claim 22, Lapierre teaches that the prenatal diagnosis comprises determining the sex of the fetus (page 1868 and Table 1).

Regarding claims 25, 26, 28-30, 33, 34, and 35, in the method of Lapierre, the amniotic fluid samples were collected in cases in which the fetus was suspected to have a chromosomal abnormality as indicated by an advanced maternal age, high levels of biochemical markers in maternal serum, or detection of a fetal ultrasound abnormality. The chromosomal abnormalities included trisomy 21, associated with Down syndrome (page 124 and Table 1).

Regarding claims 31 and 38, since the amniotic fluid was obtained from subjects having high levels of biochemical markers in maternal serum, the fetuses were at risk of a disease or condition not detectable by G-banding analysis of metaphase CGH.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bianchi (Clinical Chemistry. 2001. 47: 1867-1829) in view of Pinkel (U.S. Patent No. 6,210,878).

The teachings of Bianchi (2001) are presented above. Bianchi does not teach detecting the amniotic fluid fetal nucleic acids using a cDNA array or an oligonucleotide array.

However, Pinkel teaches methods for detecting genetic abnormalities, and particularly teaches the application of such methods to the analysis of amniotic fluid for

prenatal diagnosis (col. 9, lines 48-49), wherein target nucleic acids are detected using an array of cDNA probes (col. 9, line 50-64). Such cDNA arrays are considered to be oligonucleotide arrays since the term oligonucleotide is not defined as being of a particular length or of particular structure/composition.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Bianchi so to have detected the fetal nucleic acids using a cDNA array as taught by Pinkel because this would have allowed for the simultaneous analysis of multiple fetal nucleic acids and would have provided an effective means for detecting target fetal nucleic acids as indicative of a prenatal diagnosis.

9. Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bianchi (Clinical Chemistry. 2001. 47: 1867-1829) in view of Fan (Genome Research. 2000. 10:853-860).

The teachings of Bianchi (2001) are presented above. Bianchi does not teach detecting the amniotic fluid fetal nucleic acids using a SNP array or an oligonucleotide array.

However, Fan teaches methods for simultaneously screening for a large number of SNPs associated with genetic disorders using arrays having immobilized thereon oligonucleotide probes that are specific for SNPs. The high density tag arrays consist of over 64,000 probes (page 853) and provide for quantitative hybridization results, thereby permitting the determination of allele frequency in a DNA sample (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Bianchi so to have detected the fetal nucleic acids using the oligonucleotide SNP array taught by Fan in order to have provided a highly effective means for simultaneously screening the fetal DNA for the presence of SNPs associated with genetic diseases, thereby providing a rapid and sensitive method of prenatal diagnosis.

10. Claims 20, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bianchi (Clinical Chemistry. 2001. 47: 1867-1829) in view of Bianchi (U.S. Patent No. 5,714,325).

The teachings of Bianchi (2001) are presented above.

Regarding claim 20, Bianchi (2001) does not teach labeling the probe with a biotin label or a digoxigenin label.

However, Bianchi ('325) teaches methods of prenatal diagnosis wherein fetal nucleic acids are amplified by PCR and detected using a labeled probe (col. 14, line 13-line 26, and col. 15, lines 15-30). Bianchi also teaches labeling probes with biotin or digoxigenin (col. 18, lines 20-24, col. 20, line 62 to col. 21, line 11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Bianchi (2001) so as to have labeled the nucleic acids with biotin or digoxigenin because this would have provided an equally effective means for labeling the nucleic acids to thereby facilitate their detection.

Regarding claims 36 and 37, Bianchi (2001) doesn't teach applying the prenatal diagnosis method to the detection of an X-linked disorder such as Duchenne muscular dystrophy.

However, Bianchi ('325) teaches performing prenatal diagnosis to detect chromosome X deletions associated with Duchenne muscular dystrophy using available probes (col. 14, lines 43-63).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Bianchi (2001) to the detection of chromosome X deletions associated with Duchenne muscular dystrophy in order to have provided an effective method of prenatal diagnosis of Duchenne muscular dystrophy.

11. Claims 7, 11, 29, 32, 39-48, 51-54, 56, 59-67, 69-76, 79-88, 90-93, 96, 97, 99, 102-111, 114, 115, 117, 118, 120, and 124-127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapierre in view of Veltman et al (American Journal of Human Genetics. April 2002. 70: 1269-1276; cited in the IDS).

The teachings of Lapierre are presented above. While Lapierre teaches analyzing amniotic fluid fetal DNA by CGH analysis to provide a prenatal diagnosis, Lapierre does not teach analyzing the amniotic fluid fetal DNA by array-based CGH.

However, Lapierre does teach that the new technology of microarray CGH provides a rapid and automated screening of chromosomal abnormalities commonly found during prenatal diagnosis including aneuploidies of chromosomes 13, 18, 21 and Y, deletions observed in Wolf Hirschhorn, Cri du chat syndromes and microdeletions as

small as those observed in Prader-Willi and diGeorge syndromes (page 130, col.1). Lapierre suggests applying microarray CGH to isolated fetal DNA that has been amplified by PCR (page 130, col. 1).

Further, Veltman teaches the method of high-throughput array-based comparative genomic hybridization to detect chromosomal abnormalities. This method comprises providing a test sample having an unknown karyotype and labeled with a detectable agent; providing a reference sample of a known karyotype and labeled with a detectable agent; providing an array of genetic probes immobilized at discrete spots on an array and comprising a substantially complete third genome or a subset of a third genome; determining the binding of the test and reference samples to the genetic probes; and based on the relative binding pattern providing a diagnosis (page 1271 to page 1272). Veltman states that telomeric chromosomal rearrangements may cause mental retardation, congenital anomalies, and miscarriage (abstract). It is stated that robustness and simplicity of array-based CGH make it highly suitable for introduction into the clinic as a rapid and sensitive automated diagnostic procedure (abstract and page 1271).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lapierre so as to have performed the CGH analysis by array-based CGH in order to have achieved the advantages set forth by Lapierre and Veltman of providing a highly effective, rapid and automatable means for providing a prenatal diagnosis.

Regarding claims 29, 32, 39, 40, 42, 70, 73, 80-81, and 83, Lapierre suggests that microarray CGH analysis should be used to detect microdeletions such as those observed in Wolf Hirschhorn syndrome, Cri du chat syndrome, Prader-Willi syndrome and DiGeorge syndrome (page 130). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the microarray CGH method of Lapierre in view of Veltman to the detection of microdeletions in order to have provided a rapid and effective means for diagnosing the fetus for Wolf Hirschhorn syndrome, Cri du chat syndrome, Prader-Willi syndrome and DiGeorge syndrome.

Regarding claim 41, 82, and 107, Lapierre does not specifically teach applying the CGH analysis to prenatal diagnosis of a subtelomeric rearrangement. However, Veltman teaches that telomeric chromosomal rearrangements may cause mental retardation, congenital anomalies and miscarriages (page 1269 and abstract). Veltman teaches applying array-based CGH to the detection of subtelomeric rearrangements using an entire subtelomeric clone set (page 1272 and Figure 1). It is stated that the array-based CGH subtelomeric assay is capable of screening all human subtelomeric regions in a single hybridization assay (page 1274, col. 2). Veltman concludes that array-based subtelomeric screening will have a profound impact on the diagnosis and genetic counseling of patients with mental retardation (page 1275).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the microarray CGH analysis of Lapierre to the detection of subtelomeric rearrangements in order to have provided an effective

means for simultaneously screening for a multitude of subtelomeric rearrangements associated with mental retardation and congenital anomalies, thereby providing an effective method of prenatal diagnosis of these conditions.

Regarding claims 44-48, 90-93, and 109-111, in the array based CGH analysis of Veltman, the test and reference nucleic acids are each labeled with a fluorescent moiety of either Cy-3 or Cy-3 by random priming (page 1271, col. 2). Regarding claims 48, 93 and 111, while Veltman teaches that the test DNA is labeled with Cy3 and the reference DNA is labeled with Cy5, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified this methodology so as to have labeled with the test DNA with Cy5 and the reference DNA with Cy3 in order to have provided an equally effective means for labeling the DNAs.

Regarding claims 51-53, 96, and 114, in the array based CGH analysis of Veltman, high copy number repeats are suppressed by adding unlabeled human Cot-1 DNA to the test and reference sample prior to the contacting step (page 1271, col. 2).

Regarding claims 60, 103, and 126, Lapierre does not teach the methodology by which the karyotype of the genome of the reference nucleic acids was determined. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have determined the karyotype of the reference genome by any art conventional technique, including the techniques of G-banding, metaphase CGH, FISH or SKY because each of these techniques would have provided an effective means for characterizing the karyotype as normal. Note that the claims do not require performing an active process step of determining the karyotype of the reference

genome using the recited methods and since Lapierre and Veltman each teach that the reference genome is obtained from an individual with a normal karyotype, the methodology by which the karyotype was determined does not distinguish the claims over the prior art.

Regarding claims 61-62, 104-111, 114, 115, 117, 118, 120, and 124-127, in the array based CGH analysis of Veltman, the method further comprises measuring the intensity of the signals produced by the first and second detectable agents at the discrete spots on the array using a computer-assisted imaging system to obtain a fluorescent image of the array, and using the image analysis system to interpret the data and to display copy number ratios as a function of the genomic locus in the third genome (page 1271, col. 2 to page 1272, col. 1).

Regarding claim 63, Lapierre teaches that the prenatal diagnosis comprises determining the sex of the fetus (page 1868 and Table 1).

Regarding claims 64-65, 69-71, and 74 Lapierre teaches that the prenatal diagnosis comprises detecting trisomy 13, 18 or 21 (Table 1) and the presence of the XX or XY chromosomes.

Regarding claims 66, 67, 69-71, 74, 75, and 76, in the method of Lapierre, the amniotic fluid samples were collected in cases in which the fetus was suspected to have a chromosomal abnormality as indicated by an advanced maternal age, high levels of biochemical markers in maternal serum, or detection of a fetal ultrasound abnormality. The chromosomal abnormalities included trisomy 21, associated with Down syndrome (page 124 and Table 1).

Regarding claims 72 and 79, since the amniotic fluid was obtained from subjects having high levels of biochemical markers in maternal serum, the fetuses were at risk of a disease or condition not detectable by G-banding analysis of metaphase CGH.

Regarding claims 84-87, 90-93, 96 and 103, Lapierre teaches that the results of CGH analysis are compared to conventional cytogenetic analysis performed in situ by R-banding techniques (page 124, col. 1). Lapierre does not teach comparing the results of the CGH analysis of the test sample to a FISH analysis.

However, Veltman teaches comparing the results of array-based CGH to FISH analysis of a test sample to determine the consistency of the results, the sensitivity of detection and the selectivity of detection. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Lapierre so as to have compared the results of the array-based CGH analysis to results obtained using FISH in order to determine the consistency, sensitivity and selectivity of the detection method, in order to ensure that the accuracy of the prenatal diagnosis method.

Regarding claims 104-111, 114, 115, 117, 118, 120, 124-127, Lapierre teaches analyzing amniotic fluid fetal DNA samples from test subjects that ultrasound anomalies. Lapierre does not specifically teach analyzing amniotic fluid fetal DNA samples obtained from a fetus determined to have multiple congenital anomalies by sonographic examination, but having a normal karyotype, and particularly a normal karyotype which has been determined by a metaphase CGH analysis with a 550 band level resolution. However, Lapierre does teach that the method of array-based CGH

analysis should be used to detect microdeletions in fetal nucleic acids as indicative of genetic disorders such as Prader-Willi and DiGeorge syndromes (page 130, col. 1). Further, Veltman teaches the use of array-based CGH to detect subtelomeric chromosomal rearrangements as indicative of disorders associated with mental retardation and genetic malformations (abstract and page 1269). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the array-based CGH analysis taught by Lapierre in view of Veltman to the analysis of sample nucleic acids obtained form test and control subjects that have the normal number of chromosomes and thereby a normal karyotype in order to have provided the advantage of generating a method of prenatal diagnosis that detected microdeletions and subtelomeric rearrangements associated with genetic disorders that are not detectable by conventional karyotyping methods. Regarding claims 105 and 106, it is noted that the claims do not require an active process step of performing CGH analysis with a 550 band resolution. Further, it is noted that it is a property of the microdeletions and subtelomeric disclosed by Lapierre and Veltman that these chromosomal micro-abnormalities are not necessarily detectable by metaphase CGH analysis with a 550 band level resolution. At the time the invention was made, it was well known in the art that small chromosomal deletions or alterations could not be detected by CGH analysis of metaphase chromosomes. Accordingly, modification of the method of Lapierre so as to have detected the microdeletions or subtelomeric rearrangements by array-based CGH necessarily results in the detection of a

chromosomal abnormality that is not detectable by metaphase CGH analysis with a 550 band level of resolution.

Regarding claim 127, Lapierre does not indicate the source of the reference nucleic acids and thereby does not teach that the test and reference nucleic acids are matched for fetal gender, site of sample acquisition, gestational age, and storage time. However, Lapierre does teach that the reference/control nucleic acids are obtained from karyotypically normal samples (page 123, col. 2). Lapierre also teaches performing CGH using both reference nucleic acids that are obtained from males and from females (Figure 2 and page 126). Further, the use of matched controls was well known in the art at the time the invention was made. Since the CGH method relies on detecting the occurrence of a genetic abnormality by comparing the results of a test sample with a reference sample, the ordinary artisan would have recognized the importance of selecting matched test and reference samples for parameters which would effect the accuracy of the assay including fetal gender, means by which the amniotic fluid was obtained, gestation age and storage/handling of the amniotic fluid. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed the method of Lapierre using test and reference samples that were matched for fetal gender, site of sample acquisition, gestational age and storage time in order to have ensured that any differences observed between the test and reference samples were due to chromosomal changes, rather to non-related factors, thereby ensuring the accuracy of the prenatal diagnosis.

12. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lapierre in view of Muller (U.S. Patent No. 6,306,589).

The teachings of Lapierre are presented above. Lapierre teaches labeling the amniotic fluid nucleic acids with the fluorescent label Fluor X, but does not teach labeling the amniotic fluid nucleic acids with the fluorescent dyes of Spectrum Red or Spectrum Green.

However, Muller teaches methods of CGH analysis (col. 3, lines 54-61), wherein the test and reference nucleic acids are labeled with the fluorescent dyes Spectrum green and Spectrum red (col. 6, lines 4-14; col. 7, lines 57-63).

In view of the teachings of Muller, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lapierre so as to have labeled the test and reference nucleic acids with Spectrum green and Spectrum red dyes in place of Fluor X because this would have provided an equally effective means for labeling the nucleic acids and for facilitating the detection of the hybridization of the nucleic acid to the probes.

13. Claims 49, 50, 94, 95, 112 and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapierre in view of Veltman, and further in view of Muller (U.S. Patent No. 6,306,589).

The teachings of Lapierre and Veltman are presented above. Lapierre teaches labeling the amniotic fluid nucleic acids with a Fluor X-Amido fluorescent label, and Veltman teaches labeling test and reference nucleic acids with Cy3 and Cy5. The

combined references do not teach labeling the amniotic fluid test nucleic acids and the reference nucleic acids with the fluorescent dyes of Spectrum Red or Spectrum Green.

However, Muller teaches methods of CGH analysis (col. 3, lines 54-61), wherein the test and reference nucleic acids are labeled with the fluorescent dyes Spectrum green and Spectrum red (col. 6, lines 4-14; col. 7, lines 57-63).

In view of the teachings of Muller, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Lapierre so as to have labeled the test and reference nucleic acids with Spectrum green and Spectrum red dyes because this would have provided an equally effective means for labeling the nucleic acids and for facilitating the detection of the hybridization of the nucleic acid to the array of probes.

14. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lapierre in view of Sammons et al (U.S. Patent No. 5,948,278).

The teachings of Lapierre are presented above. Lapierre teaches obtaining the amniotic fluid sample from woman of "advanced maternal age" but does not specifically teach that the woman are age 35 or older.

Sammons teaches that amniocentesis increases a woman's risk of miscarriage and therefore amniocentesis is generally offered primarily to woman over the age of 35 since woman over the age of 35 have a statistically greater probability of bearing children with congenital defects (col. 1, lines 43-49).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have specifically obtained the amniotic fluid samples

from pregnant woman over the age of 35 because these woman would be at a greater risk of having fetuses with a genetic abnormality, and thereby would benefit most from prenatal diagnosis.

15. Claims 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lapierre in view of Veltman and Sammons et al (U.S. Patent No. 5,948,278).

The teachings of Lapierre and Veltman are presented above. Lapierre teaches obtaining the amniotic fluid sample from woman of "advanced maternal age" but does not specifically teach that the woman are age 35 or older.

Sammons teaches that amniocentesis increases a woman's risk of miscarriage and therefore amniocentesis is generally offered primarily to woman over the age of 35 since woman over the age of 35 have a statistically greater probability of bearing children with congenital defects (col. 1, lines 43-49).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have specifically obtained the amniotic fluid samples from pregnant woman over the age of 35 because these woman would be at a greater risk of having fetuses with a genetic abnormality, and thereby would benefit most from prenatal diagnosis.

16. Claims 55, 57, 98, 100, 116, 119, and 121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapierre in view of Veltman and further in view of Bianchi (Clinical Chemistry. Oct. 2001. 47: 1867-1869; cited in the IDS of May 10, 2007).

The teachings of Lapierre and Veltman are presented above.

In particular, Lapierre teaches a method of prenatal diagnosis wherein the sample of amniotic fluid fetal DNA is obtained by removing a first portion of amniotic cells from an amniotic fluid sample to obtain a remaining amniotic material and treating the remaining 5-10 ml of amniotic fluid to extract high molecular weight DNA for CGH analysis (page 124, col. 1). The remaining amniotic fluid thereby contained both amniotic cells and cell free fetal DNA. Lapierre does not teach a method wherein the amniotic fluid sample is obtained by removing substantially all of the cells to obtain cell free DNA.

However, Bianchi teaches a method of prenatal diagnosis comprising obtaining an amniotic fluid sample from pregnant woman at 16-20 weeks of gestation, isolating DNA present in the amniotic fluid sample, performing real-time quantitative PCR using primers and a dual-labeled fluorescent TaqMan probe, and determining the sex of the fetus, thereby providing a prenatal diagnosis (page 1867, col. 2 and page 1868, col. 1). Bianchi teaches that the amniotic fluid fetal DNA is obtained by providing the amniotic fluid sample from a pregnant woman, removing cells from the sample by centrifugation, and treating the remaining amniotic fluid so as to extract cell-free DNA (page 1867, col. 2). The centrifugation step removes substantially all of the cells from the amniotic fluid so that the amniotic fluid fetal DNA consists essentially of cell-free fetal DNA. Further, Bianchi teaches that the amniotic fluid samples are first frozen, stored under appropriate conditions, thawed at 37C prior, and remaining cells are removed by centrifugation prior to treatment to extract DNA (page 1867, col. 2). Bianchi teaches that amniotic fluid contains 100 to 200 fold more fetal DNA per millimeter as compared to maternal plasma

(page 1868, col. 1). Bianchi states that "This higher amount may permit new studies and clinical applications to be performed on this typically discarded material" (page 1868, col. 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lapierre so as to have treated the amniotic fluid as taught by Bianchi and to thereby have performed the prenatal diagnosis method using cell-free fetal DNA because Bianchi teaches that amniotic fluid comprises large quantities of cell-free fetal DNA and thereby this would have provided a highly effective source of fetal DNA for prenatal analysis and a convenient source of fetal DNA since the amniotic fluid supernatant is often available but discarded when the amniotic fluid has been obtained for alternative forms of analysis.

17. Claims 58, 101, 122 and 123 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapierre in view of Veltman and Bianchi, and further in view of Shah (U.S. Patent No. 6,916,621).

The teachings of Lapierre, Veltman and Bianchi are presented above.

Lapierre teaches using random priming to label the test and reference nucleic acid samples (page 1271, col. 2), but does not teach amplifying the test and reference (i.e., control) nucleic acids by PCR.

However, Bianchi teaches amplifying the amniotic fluid fetal DNA by PCR using primers prior to performing probe hybridization (page 1868, col. 1). Additionally,

Veltman teaches amplifying the cloned DNA used as probes by degenerate oligonucleotide primed-PCR (DOP-PCR; page 1272, col. 1).

Shah (col. 15, lines 10-42) teaches methods of array-based CGH analysis wherein the sample (i.e., test and reference/control) nucleic acids are amplified by PCR. Shah teaches that degenerate primers can be used to amplify the sample nucleic acids in order to incorporate a labeled nucleotide into the nucleic acids. It is stated that PCR can be used in place of random primer extension to label nucleic acids (col. 15, lines 10-16).

In view of the teachings of Shah that it was conventional in the art to use PCR in place of random priming to label nucleic acids, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lapierre so as to have amplified the test and reference (control) nucleic acids by PCR prior to performing the array-based CGH analysis in order to have provided an alternative means for incorporating the label into the test and reference (control) nucleic acids to achieve the benefit of providing labeled target and reference nucleic acids to thereby facilitate their detection. Moreover, in view of the teachings of Veltman of using DOP-PCR to increase the quantity of nucleic acids, the teachings of Shah to amplify the test and control/reference nucleic acids and the teachings of Bianchi to use PCR to specifically increase the quantity of particular target nucleic acids in amniotic fluid, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lapierre so as to have amplified the test and reference (control) nucleic acids by PCR prior to performing the array-based CGH

analysis in order to have increased the quantity of these nucleic acids thereby improving the sensitivity of detection in the method of prenatal diagnosis.

18. Claims 77 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapierre in view of Veltman and further in view of Bianchi (U.S. Patent No. 5,714,325).

The teachings of Lapierre and Veltman are presented above. The combined references do not teach applying the prenatal diagnosis method to the detection of an X-linked disorder such as Duchenne muscular dystrophy.

However, Bianchi ('325) teaches performing prenatal diagnosis to detect chromosome X deletions associated with Duchenne muscular dystrophy using available probes (col. 14, lines 43-63).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Lapierre in vie w of Veltman to the detection of chromosome X deletions associated with Duchenne muscular dystrophy in order to have provided an effective method of prenatal diagnosis of Duchenne muscular dystrophy.

19. Claim 89 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lapierre in view of Veltman and further in view of Pinkel (U.S. Patent No. 5,665,549; cited in the IDS).

The teachings of Lapierre and Veltman are presented above. The combined references do not teach applying the prenatal diagnosis method to the detection of a deletion of chromosome 15q11-q13.

However, Lapierre does teach applying array based CGH analysis to the detection of microdeletions observed in Prader-Willi syndrome.

Further, Pinkel teaches methods for detecting chromosomal abnormalities using CGH analysis. Pinkel teaches that the deletion of 15q11-q13 sequences are associated with the occurrence of Prader-Willi syndrome (col. 2, lines 17-21).

In view of the teachings of Lapierre of applying array-based CGH analysis to the detection of deletions associated with Prader-Willi syndrome and the teachings of Pinkel that Prader-Willi syndrome occurs as a result of a deletion of 15q11-q13 sequences, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lapierre so as to have applied the array-based CGH analysis to the detection of the deletion of 15q11-q13 chromosomal sequences in order to have provided an effective means of prenatal diagnosis of Prader-Willi syndrome.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Carla Myers/

Primary Examiner, Art Unit 1634